ISSN: 2755-0141

Japan Journal of Clinical & Medical Research

SCIENTIFIC Research and Community

Review Article

Open Access

Are Stromal Tumor - Reactive Plasma Cells in Mesopharyngeal Squamous Cell Carcinoma a Prognostic Positive Biomarker with Immunomodulatory Potential - A Clinical Case from our Practice

Lena Marinova*, Vaska Vasileva, Evgenia Todorova, Nikolai Kahciev and Katia Sergieva

Medical Oncology Clinic, Radiation and Metabolic Brachytherapy Compartment, UMHAT "Queen Joanna" Sofia, Bulgaria

ABSTRACT

Tumour-reactive plasma cells (TRPCs) are part of the tertiary lymphoid structures (TLSs) and have been reported to be positively associated with the long-term survival of patients with various cancers.

We present an inoperable mesopharyngeal squamous cell carcinoma with pronounced stromal tumor-reactive plasma cells infiltration or tumour- infiltrating plasma cells (TIP), which made the pathohistological diagnosis difficult in a 50-year-old patient. Due to the extreme hardness of the tumor, the three biopsies were insufficient material, necessitating the performance of immunohistochemical (IHC) analysis, making the final diagnosis - Undifferentiated squamous cell carcinoma /G3, without keratinization with an abundant plasma cell stromal reaction. A complex treatment was carried out, including preoperative intensity modulated radiotherapy (IMRT) up to total dose 45 Gy, followed by radical tumor resection with clear of tumor cells resection lines and bilateral selective dissection of the suspected metastatic cervical lymph nodes.

Against the background of this clinical case, we present the rarely observed peritumoral tertiary lymphoid structures in mesopharyngeal squamous cell carcinoma, characterized by single tumor cells surrounded by fibrous tissue and an inflammatory infiltrate rich in plasmacytic cells. Our observations regarding the presence of TLSs in an inoperable locally advanced mesopharyngeal tumor confirm increased antitumor immunity that improves treatment outcomes, namely that we were able to achieve local tumor control after preoperative radiotherapy up to TD 45 Gy and salvage surgery.

***Corresponding author**

Lena Marinova, Medical Oncology Clinic, Radiation and Metabolic Brachytherapy Compartment, UMHAT "Queen Joanna" Sofia, Bulgaria.

Received: January 07, 2025; **Accepted:** January 10, 2025; **Published:** January 20, 2025

Keywords: Mesopharyngeal Squamous Cell Carcinoma, Tumour-Infiltrating Plasma Cells (TIP), Tertiary Lymphoid Structures (TLS), Preoperative Radiotherapy, TLS Immunomodulation

Introduction

Tumour-reactive plasma cells (TRPCs) have been reported to be positively associated with the long-term survival of patients with various cancers [1]. Univariate and multivariate Cox regression analysis, together with survival analysis of the interaction between TIP and other variables, confirmed tumour- infiltrating plasma cells (TIP) to be a significant and independent prognostic factor for overall survival of esophageal squamous cell carcinoma [2]. Tumour-infiltrating B cells, including B cells and plasma cells, could form tumour-associated immune aggregates from small unorganized clusters to tertiary lymphoid structures (TLSs) [3]. Tertiary lymphoid structures (TLS) are clusters of specialized immune cells (B cells, T cells, dendritic cells, stromal cells, etc.) that form in and around a tumor [4]. TLS are ectopic lymphoid aggregates that reflect lymphoid neogenesis occurring in tissues at sites of inflammation [5]. Plasma cells, an important role in humoral immunity, seem to be underestimated in anti-tumour response, which promote the formation of TLSs, secret IgG1, drive cytotoxic T-cell responses [6]. TLS are elegantly regulated and complex structures which may be exploited to promote patient survival and response to immunotherapy [4]. The presence of tumour-associated B cells in various cancer types, including breast, liver, colon, and others, has shown a positive correlation with improved prognosis [7-9]. We present an inoperable mesopharyngeal squamous cell carcinoma with pronounced stromal TRPCs infiltration, which made the pathohistological diagnosis and assessment of the necessary complex treatment difficult in a 50 year-old patient.

Clinical Case

It concerns a 50 year-old man with difficulty in taking liquid and solid food since the beginning of 2023. At the end of 2024 Computed tomography (CT) scan of the oral cavity, larynx and pharynx revealed an oval, relatively well-demarcated soft tissue formation with dimensions of 37/43/32 mm. The lesion is located sagittally and parasagittally more to the left and with its lower pole reaches the epiglottis. With its anterior contour, the lesion is subject to the palatine and lingual tonsils, without a clear border between the formation and the muscles of the floor of the oral cavity. The lesion does not increase in density after contrast. The lymph nodes on both sides of the neck are rounded with a diameter of up to 10 mm. Conclusion: Tumor in the mesopharynx with nonspecific bilateral lymphadenopathy (Figure 1).

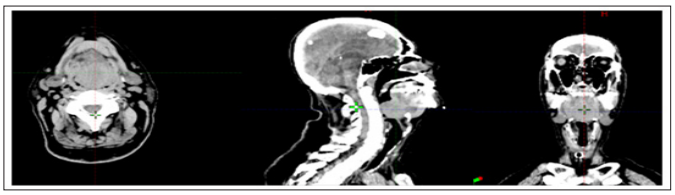

Figure 1: CTscan of the Oral Cavity, Larynx and Pharynx Revealed an Oval Relatively Well-Circumscribed Soft Tissue Mass Measuring 37/43/32mm. The Lesion is Located Sagittally and Parasagittally and with its Lower Pole Reaches the Epiglottis

Local Status

A hyperemic mucous membrane of the oropharynx with a thick secretion on the posterior pharyngeal wall is noted. A large exophytic tumor was visualized involving the base of the tongue and reaching the epiglottis, which did not allow a good view of the laryngeal structures. Bilaterally enlarged cervical lymph nodes are not palpated on the neck. Three consecutive biopsies were taken from the tumor formation, but due to its extreme hardness, they were of insufficient material for the pathologist to answer - Microinvasive squamous cell carcinoma with abundant plasma cell stromal reaction. The patient is presented to the Oncology Committee for assessment of the necessary complex treatment. As this was an unresectable mesopharyngeal tumor/cT3 cN0 cM0, despite a histological result consistent with microinvasive squamous cell carcinoma, it was considered amenable to preoperative radiotherapy (RT) after a tracheostomy, due to an obstructed upper airway, followed by consideration of salvage surgery. In March 2024, the patient started intensity modulated radiotherapy (IMRT) in the tumor area up to a total dose (TD) of 68 Gy with an insurance zone of 0.7 cm up to TD 66 Gy, as well as in the cervical lymph basin bilaterally up to TD 60 Gy (Figure 2, Figure 3). The insufficient biopsy material was sent to the Specialized Hospital for Active Treatment of Hematological Diseases for immunohistochemical (IHC) examination. From there we got the following morphological description: A hyperplastic overgrown squamous mucosa with low-grade epithelial dysplasia and paradoxical maturation with a transition to invasive squamous cell carcinoma, partly keratinizing, but with an aversive pattern of infiltration into the subepithelial space in the form of weakly cohesive patches or groups of 3-5 cells, whose identification is difficult, is visualized from a far more intensely presented non-specific inflammatory infiltrate, rich in lymphocytes arranged in follicles, macrophages, granulocytes, plasma cells, and scattered necrotic and karyorectic foci. A fibrosing chronic inflammatory process is also visualized, as well as fibrous tissue, plasma cells, cells with an unspecified cytological detail due to a serious traumatic artifact. Immunohistochemistry showed: for CD2 and CD7 - positive immunolabeled individual lymphocytes, for CD56 - negative labeling in one of the materials and positive immunolabeling of single cells in the other material, for CD20 - positive immunolabeled individual lymphocytes, for MCK and CK 5/6 - positively immunolabeled infiltrative carcinoma epithelial composition. The radiation treatment was performed when the patient had severe feeding difficulties, which necessitated the intravenous infusion of water-salt solutions and nutritional supplements. The patient's weight is reduced by 10 kg. When comparing the beam volume verification during RT, performed with cone beam computed tomography (CB/CT), it was found that there was no significant difference in the tumor volume at the RT beginning (A), in the RT middle (B) and at the end of RT (C) (Figure 4). The above circumstances necessitated a decision to stop IMRT until the realization of TD in the tumor (GTV) 45.3Gy with dayli dose (DD) 2.06Gy, in the insurance zone (CTVp) up to TD 44Gy, and in the retropharyngeal and cervical lymph nodes from the first to fourth level (CTVn) up to TD 42Gy, which is sufficient preoperative RT dose. The patient was referred for salvage surgery. In May 2024, resection of the tumor was performed with bilateral selective lymph node dissection of the suspected metastatic lymph nodes. Intraoperatively: A tumor involving the base of the tongue was found. A suture dissection was performed on the left, removing suspicious for metastatic lymph nodes from zone 2A, 2B, and zone 5. After dissection of the submental muscles, a tumor involving the base of the tongue was reached. The latter was removed and then switched to plastic. A nasoesophageal tube was placed, then a cervical dissection was performed on the right, dissecting suspicious for metastatic lymph nodes from zone 2A, 2B, and zone 5. Histological result - Core material from the mesopharyngeal tumor (tumor size up to 5 cm) - Histological morphology of undifferentiated squamous cell carcinoma (G3), without keratinization with abundant plasma cell stromal reaction. The marginal resection lines are without tumor infiltration, the dissected lymph nodes in the left and right neck with chronic lymphadenitis. Immunohistochemistry- A panCK-positive immunolabeled infiltrative carcinoma epithelial composition, CD 138-positive immunolabeled reactive plasma cells - kappa and lambda light chains in a 1:1 ratio were reported in the core tumor material and peritumoral infiltrates of CD 20 positive B cells. Postoperatively, a discussion was held about the subsequent therapeutic behavior, considering the patient to remain under long-term observation. Given the clear resection lines of tumor cells and the absence of metastatic lymph nodes, as well as the abundant plasma cell stromal reaction present, the patient did not require adjunctive postoperative RT. After 5 months of the surgery, at the end of October, the patient underwent PET/CT with the following result - Head and neck - State after radiotherapy of a tumor formation in the mesopharynx with subsequent resection of the base of the tongue and neck dissection. At the level of the root of the tongue, an operative defect is visualized on the left, diffuse discrete over-background activity and edema of the soft tissues - tongue, submandibular glands, subcutaneous fat tissue, caudal muscles. Inactive lymph nodes are imaged bilaterally with reference margins. In the area of the pharynx, including the oropharynx, no pathological foci were observed locally, background metabolic activity was detected. The pharynx is presented normally passable along its entire length, epiglottis with normal imaging. No pathologically active lesions in the cervical lymph nodes. Symmetrically functionally increased metabolic activity in occipital skeletal muscle. Conclusion - PET/CT data for a complete therapeutic response of the treated tumor. No data on metastatic dissemination. The patient is subject to long-term monitoring through monthly control examinations, as well as restaging PET/CT scan every 6 months.

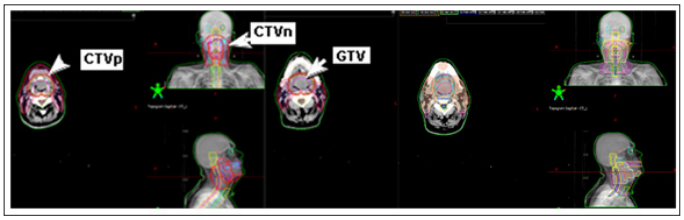

Figure 2: Contouring of the Target Volumes (GTV, CTVp and CTVn) Subject to Radiotherapy

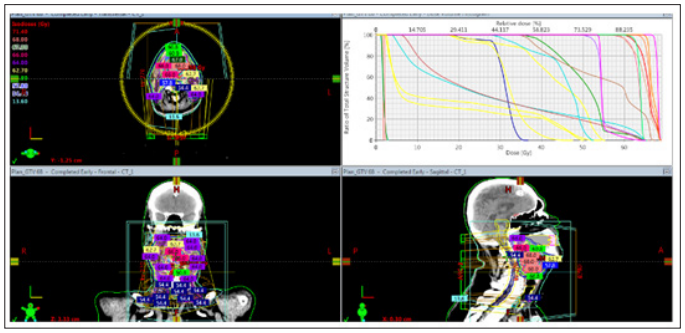

Figure 3: Intensity Modulated Radiotherapy (IMRT) by the VMAT Method in the Tumor area up to a Total Dose (TD) of 68 Gy with an Insurance Zone of 0.7 cm up to td 66 Gy, as well as in the Cervical Lymph Basin Bilaterally up to td 60 Gy

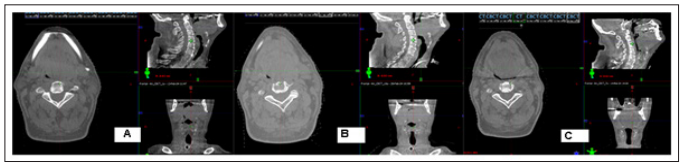

Figure 4: When Comparing the Beam Volume Verification During Irradiation, Performed with Cone Beam Computed Tomography (CB/CT), it was Found that there was no Significant Difference in the Tumor Volume at the RT Beginning (A), in the Middle (B) and at the End of RT (C).

Discussion

Strong anti-tumor immune responses are achieved through the interplay between innate and adaptive immune cells which drive the expansion and activation of tumor antigen-specific cytotoxic T cells and the production of antibodies by plasmablasts and plasma cells collectively termed antibody-secreting cells (ASCs)[10]. Tertiary lymphoid structures (TLSs) are organized, nonencapsulated aggregates of lymphoid cells that form in nonlymphoid tissues under pathological conditions after birth [11,12]. De novo TLS formation in tumors requires optimal cytokine and chemokine concentration and specialized immune cell types [13].

Head and neck squamous cell carcinoma (HNSCC), the most predominant subtype among head and neck tumors, has shown a better prognosis and a greater response to immunotherapy when associated with TLSs [14]. These findings underscore TLSs significance in enhancing antitumor immunity and improving patient outcomes in the context of HNSCC, particularly in the HPV− subgroup [15].

The strange situation in the presented inoperable mesopharyngeal tumor was that in a large exophytic formation, adequate biopsy was not possible due to its extremely firm consistency. Our concern was that the pathohistological response was microinvasive carcinoma, which did not correspond to the visible locally advanced inoperable tumor, which was possibly benign. Because of the minimal amount of tumor cells and the abundant peritumoral inflammatory component with the presence of plasma cells, immunohistochemical analysis was necessary to rule out hematologic disease, including lymphoma or extramedullary plasmacytoma.

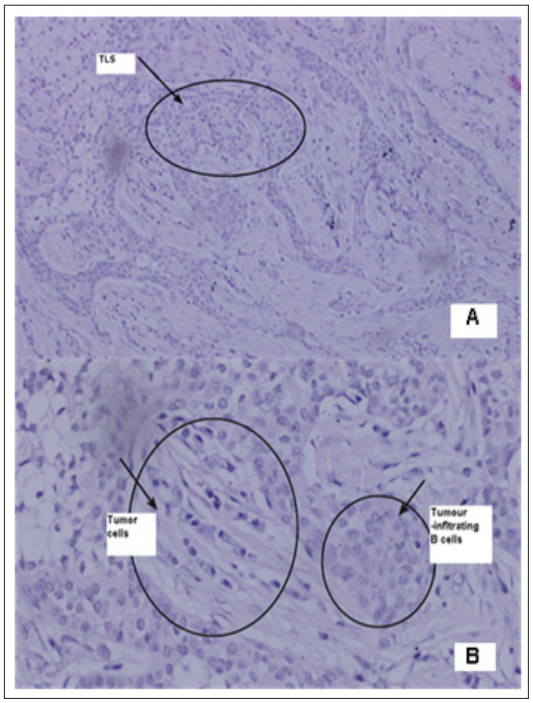

Figure 5: Pathohistological Morphology of Squamous Cell Carcinoma without Keratinization with Abundant Plasma Cell Stromal Reaction

A hyperplastic overgrown squamous mucosa with low-grade epithelial dysplasia and paradoxical maturation with a transition to invasive squamous cell carcinoma, partly keratinizing, but with an aversive pattern of infiltration into the subepithelial space in the form of weakly cohesive patches or groups of 3-5 cells, whose identification is difficult, is visualized from a far more intensely presented non-specific inflammatory infiltrate, rich in lymphocytes arranged in follicles, macrophages, granulocytes, plasma cells, and scattered necrotic and karyorectic foci (TLS). A/ H&E x200; B/ H&E x 400.

Due to the fact that the mesopharyngeal tumor was inoperable, we decided to start preoperative RT, which was accompanied by pronounced radiation reactions, making it even more difficult for the patient to eat. In addition to the difficult tolerability of radiation treatment, we found that there was no pronounced tumor reduction and it was clearly a radiation-resistant tumor that would not be significantly affected by the planned RT (Figure 4). Although in locally advanced mesopharyngeal carcinomas it is not possible to perform a radical tumor operation with clean resection lines, in the presented clinical case a salvage tumor resection was required. Hematoxylin and eosin (H&E) staining of tissue sections allows for the evaluation of TLS size, density, and maturity, including the formation of lymphocyte clusters [16,17]. The operative material showed the strange pathohistological finding with the presence with an aversive pattern of infiltration into the subepithelial space in the form of weakly cohesive patches or groups of 3-5 cells, whose identification is difficult, is visualized from a far more intensely presented non-specific inflammatory infiltrate, rich in lymphocytes arranged in follicles, macrophages, granulocytes, plasma cells, and scattered necrotic and karyorectic foci (TLS) (Figure 5).

The prognostic value of TLSs has been widely discussed. In conditions that require an enhanced immune response, such as cancer and infectious diseases, the presence and maturation of

TLSs generally indicate more favorable outcomes [13,16,18-20]. In 1992, Louis Picker and Eugene Butcher formally introduced the concept of "tertiary lymphoid organs" (TLOs) or "tertiary lymphoid tissues" (TLTs) [7]. Several groups have revealed that, in addition to this pathway, in some tumors, an adaptive immune response is generated in situ [21].

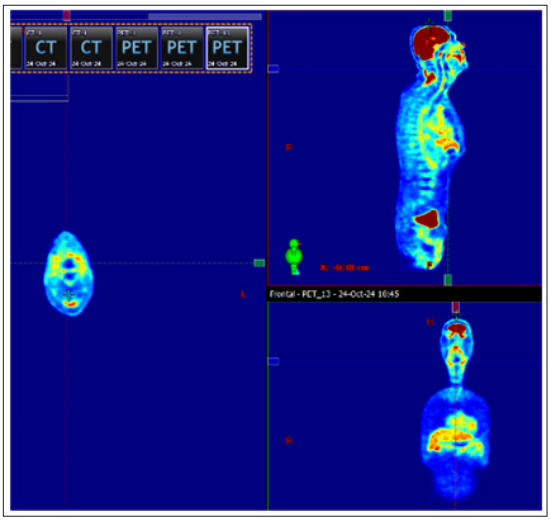

Figure 6: PET/CT Scan after 5 Months of the Complex Treatment Completion - PET/CT Data for Complete Therapeutic Response of the Mesopharyngeal Tumor. no Data on Metastatic Dissemination

The widely discussed prognostic value of TLS explains our observations, namely that radical tumor resection was possible in the presented radioresistant tumor and no regional lymph node metastases were detected despite the advanced local status. In scenarios necessitating an enhanced immune response, such as in cancer and infectious diseases, the presence and maturation of TLSs generally signify more favorable outcomes [15,22,23]. TLS have been detected in numerous tumor types using immunohistochemistry or chemokine gene signatures which tightly correlated with the presence of TLS identified by immunochemistry [24-27]. Increased B cells in pre-treatment HNSCC biopsy samples correlate with prolonged benefit from PD-1-based immunotherapy and could further enhance the predictive value of PD-L1 expression [28].

Li and colleagues endeavored to examine this issue in oral squamous cell carcinoma. They found that the presence of TLS was associated with increased 5 years overall- and relapse-free survival, and importantly, both immature and mature TLS conveyed equally positive outcomes [29]. In particular, mature TLS containing germinal centers had a more positive prognostic outcome compared with immature TLS [30]. Intratumoral and peritumoral TLSs at different stages of maturity are present in human laryngeal cancer, and the formation of follicle-like (FL)-TLSs is associated with a better prognosis [31]. Tumour-reactive antibodies (TRAs), which exist in both patient serum and the tumour microenvironment, have the capacity to recognise a wide range of antigens. Tumour antigens mainly include tumour-associated antigens (TAAs) and tumour-specifc antigens (TSAs) [1]. TSAs are immunogenic peptides that originate from viral open reading frames (oncogenic viral antigens) or somatic mutations (neoantigens) rather than proteins expressed by the normal human genome [32,33].

The finding that TLSs are associated with better prognosis in some types of cancer has led to the design of therapeutic strategies based on promoting the formation of these structures [34]. Mature TLSs are characterized by a rich composition of proliferating B cells, plasma cells, CD4+ helper T cells, B memory cells, and Th17 cells, and are correlated with an increased infiltration rate of CD8+ T cells [35]. Patients with mature or high-density TLSs show better prognoses in cancers after neoadjuvant chemoimmunotherapy [36]. Patients with follicle-like-TLSs exhibit increased immune cell infiltration and demonstrate markedly improved responses to immunotherapeutic approaches, further highlighting the potential of TLSs as a biomarker for predicting treatment outcomes and guiding therapeutic strategies in HNSCC [31]. Three independent studies published in 2020 showed that B cells and TLSs are important factors influencing the immune checkpoint inhibition response and that TLSs are a potential effective marker for the selection of patients for immune checkpoint inhibitors (ICIs) [13,20,37].

In the presented inoperable mesopharyngeal carcinoma, if we had more histological evidence of the presence of peritumoral TLS, we should have started the treatment with neoadjuvant immunotherapy followed by surgery. We consider that such tumors are resistant to radiotherapy (Figure 4).

A series of clinical studies have demonstrated that TLSs can significantly enhance the survival of tumor patients, especially as markers of immunotherapy [38]. Recent articles have demonstrated the value of TLSs as a prognostic indicator of disease, particularly cancer [5]. TLS, also known as tertiary lymphoid organs or ectopic lymphoid structures, is organized aggregates of immune cells that arise postnatally in nonlymphoid tissues [39]. Our observations regarding the presence of TLSs in an inoperable locally advanced mesopharyngeal tumor confirm increased antitumor immunity that improves treatment outcomes, namely that we were able to achieve local tumor control after preoperative radiotherapy up to TD 45 Gy and salvage surgery. After 5 months of the surgery, the patient underwent PET/CT which revealed a complete therapeutic response without evidence of lymphatic and hematogenous dissemination (Figure 6).

Conclusion

Literature data provide sufficient evidence for the immunomodulatory role of both immature and mature peritumoral lymphoid-like structures in different types of carcinomas. Against the background of our clinical case, we present the need to apply neoadjuvant immunotherapy in such difficult-to-diagnose and differential diagnosis carcinomas, requiring sufficient biopsy material to immunohistochemically prove the presence of B cells and TLS.

References

1. Peng Chen, Yiwei Chu, Ronghua Lin (2024) Tumor reactive plasma cells in antitumor immunity: current insights and future progress. Immunotherapy Advances 4: 1-7.
2. Chengyun Yao, Hongliang Yu, Guoren Zhou, Jianhua Xu, Dayong Gu, et al. (2021) Tumor-infiltrating plasma cells are the promising prognosis marker for esophageal squamous cell carcinoma. Esophagus 18: 574-584.
3. Kroeger DR, Milne K, Nelson BH (2016) Tumor-infltrating plasma cells are associated with tertiary lymphoid structures, cytolytic T-cell responses, and superior prognosis in ovarian cancer. Clin Cancer Res 22: 3005-3015.
4. MacFawn IP, Bruno TC (2024) Tertiary Lymphoid Structure Formation and Function in the Tumor Microenvironment. Handbook of Cancer and Immunology 1-31.
5. Sautès-Fridman C, Lawand M, Giraldo NA, Kaplon H, Germain C, et al. (2016) Tertiary lymphoid structures in cancers: prognostic value, regulation, and manipulation for therapeutic intervention. Front Immunol 7: 407.

6. Sharonov GV, Serebrovskaya EO, Yuzhakova DV, Britanova OG, Chudakov DM, et al. (2020) B Cells, plasma cells and antibody repertoires in the tumour microenvironment. Nat Rev Immunol 20: 294-307.
7. Garaud S, Buisseret L, Solinas C, Gu-Trantien C, Wind AD, et al. (2019) Tumor infltrating B-cells signal functional humoral immune responses in breast cancer. JCI Insight 5: e129641.
8. Shi JY, Gao Q, Wang ZC, Zhou J, Wang XY, et al. (2013) Margin-infltrating CD20(+) B cells display an atypical memory phenotype and correlate with favorable prognosis in hepatocellular carcinoma. Clin Cancer Res 19: 5994-6005.
9. Berntsson J, Nodin B, Eberhard J, Micke P, Jirström K (2016) Prognostic impact of tumour-infltrating B cells and plasma cells in colorectal cancer. Int J Cancer 139: 1129-1139.
10. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ (2011) Natural innate and adaptive immunity to cancer. Annu Rev Immunol 29: 235-271.
11. Gago da Graça C, van Baarsen LGM, Mebius RE (2021) Tertiary lymphoid structures: diversity in their development, composition, and role. J Immunol 206: 273-281.
12. Schumacher TN, Thommen DS (2022) Tertiary lymphoid structures in cancer. Science 375: eabf9419.
13. Helmink BA, Reddy SM, Gao J, Zhang S, Basar R, et al. (2020) B cells and tertiary lymphoid structures promote immunotherapy response. Nature 577: 549-555.
14. Jing Zhu, Hui Lu, Kongcheng Wang, Baorui Liu, Jing Yan (2024) Tertiary lymphoid structures in head and neck squamous cell carcinoma. Translational Oncology 44: 101949.
15. Zhang B, Hao Li , Yuan-Tong Liu, Xiong D, Zhang L, et al. (2023) Single-cell chemokine receptor profiles delineate the immune contexture of tertiary lymphoid structures in head and neck squamous cell carcinoma. Cancer Lett 558: 216105.
16. Calderaro J, Petitprez F, Becht E, Laurent A, Hirsch TZ, et al. (2019) Intra-tumoral tertiary lymphoid structures are associated with a low risk of early recurrence of hepatocellular carcinoma. J Hepatol 70: 58-65.
17. You X, Koop K, Weigert A (2023) Heterogeneity of tertiary lymphoid structures in cancer. Front Immunol 14: 1286850.
18. Soizic Garaud, Pawel Zayakin, Laurence Buisseret, Undine Rulle, Karina Silina, et al. (2018) Antigen specificity and clinical significance of IgG and IgA autoantibodies produced in situ by tumor-infiltrating B cells in breast cancer. Front Immunol 9: 2660.
19. Ayana T Ruffin, Anthony R Cillo, Tracy Tabib, Angen Liu, Sayali Onkar, et al. (2021) B cell signatures and tertiary lymphoid structures contribute to outcome in head and neck squamous cell carcinoma. Nat Commun 12: 3349.
20. Petitprez F, Reyniès dA, Keung EZ, Chen TWW, Sun CM, et al. (2020) B cells are associated with survival and immunotherapy response in sarcoma. Nature 577: 556-560.
21. Jacquelot N, Seillet C, Vivier E, Belz GT (2022) Innate lymphoid cells and cancer. Nat Immunol 23: 371-379.
22. Yumeng Wang, Huan Lin, Ningning Yao, Xiaobo Chen, Bingjiang Qiu, et al. (2023) Computerized tertiary lymphoid structures density on H&E images is a prognostic biomarker in resectable lung adenocarcinoma. Iscience 26: 107635.
23. Gwendalyn J Randolph, Shashi Bala, Jean-François Rahier, Michael W Johnson, Peter L Wang, et al. (2016) Lymphoid aggregates remodel lymphatic collecting vessels that serve mesenteric lymph nodes in Crohn disease. Am J Pathol 186: 3066-3073.
24. De Chaisemartin L (2011) Characterization of chemokines and adhesion molecules associated with T cell presence in tertiary lymphoid structures in human lung cancer. Cancer Res 71: 6391-6399.
25. Messina JL (2012) 12-Chemokine gene signature identifies lymph node-like structures in melanoma: potential for patient selection for immunotherapy? Sci Rep 2: 765.
26. Coppola D (2011) Unique ectopic lymph node-like structures present in human primary colorectal carcinoma are identified by immune gene array profiling. Am J Pathol 179: 37-45.
27. Tokunaga R (2020) 12-Chemokine signature, a predictor of tumor recurrence in colorectal cancer. Int J Cancer 147: 532-541.
28. Gavrielatou N, Fortis E, Spathis A, Anastasiou M, Economopoulou P, et al. (2023) B-cell infiltration is associated with survival outcomes following programmed cell death protein 1 inhibition in head and neck squamous cell carcinoma. Ann Oncol 35: 340-350.
29. Li Q, Liu X, Wang D, Wang Y, Lu H, et al. (2020) Prognostic value of tertiary lymphoid structure and tumour infiltrating lymphocytes in oral squamous cell carcinoma. Int J Oral Sci 12: 24.
30. Jacquelot N, Tellier J, Nutt St, Belz Gt (2021) Tertiary lymphoid structures and B lymphocytes in cancer prognosis and response to immunotherapies. Oncoimmunology 10: 1900508.
31. Haifeng Liang, Zhigang Zhang, Zhong Guan, Shibie Zheng, Jintao Lou, et al. (2023) Follicle-like tertiary lymphoid structures: a potential biomarker for prognosis and immunotherapy response in patients with laryngeal squamous cell carcinoma. Front Immunol 14: 1096220.
32. Liu XS, Mardis ER (2017) Applications of immunogenomics to cancer. Cell 168: 600-612.
33. Hu Z, Ott PA, Wu CJ (2018) Towards personalized, tumour-specifc, therapeutic vaccines for cancer. Nat Rev Immunol 18: 168-182.
34. Esparcia Pinedo L, Romero Laorden N, Alfranca A (2023) Tertiary lymphoid structures and B lymphocytes: a promising therapeutic strategy to fight cancer. Front Immunol 14: 1231315.
35. Yihong Ling, Jian Zhong, Zelin Weng, Guangrong Lin, Caixia Liu, et al. (2022) The prognostic value and molecular properties of tertiary lymphoid structures in oesophageal squamous cell carcinoma. Clin Transl Med 12: e1074.
36. Xiaoyan Sun, Weiran Liu, Leina Sun, Huilan Mo, Yingnan Feng, et al. (2022) Maturation and abundance of tertiary lymphoid structures are associated with the efficacy of neoadjuvant chemoimmunotherapy in resectable non-small cell lung cancer. J Immunother Cancer 10: e005531.
37. Rita Cabrita, Martin Lauss, Adriana Sanna, Marco Donia, Mathilde Skaarup Larsen, et al. (2020) Tertiary lymphoid structures improve immunotherapy and survival in melanoma. Nature 577: 561-565.
38. Jing Zhu, Hui Lu, Kongcheng Wang, Baorui Liu, Jing Yan (2024) Tertiary lymphoid structures in head and neck squamous cell carcinoma. Translational Oncology 44: 101949.
39. Schumacher TN, Thommen DS (2022) Tertiary lymphoid structures in cancer. Science 375: eabf9419.